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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------------|---------------------|------------------|
| 09/741,272 | 12/19/2000 | Charles Raymond Degenhardt | 8371 | 6508 |

27752 7590 12/31/2001

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EXAMINER

MCKENZIE, THOMAS C

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 12/31/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/741,272

Applicant(s)

DEGENHARDT ET AL

Examiner

Thomas McKenzie Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 December 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 6,8,10,14,16 and 17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5,7,9,11-13 and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2. 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to an application filed on 10/17/00. There are seventeen claims pending and eleven under consideration. Claims 1-5, 7, 9, and 12 are compound claims. Claim 13 is a composition claim. Claim 15 is a use claims. This is the first action on the merits. The application concerns some 2-piperidinylcarbonyl-piperidines.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:
- I. Claims 6, 8, and 10, drawn to piperazines, compounds of formula given in claim 1 with $C(O)NR^2R^3$ forming a 1-carbonylpiperazine, classified in class 544, subclasses 364, 370, and 372, among others.
 - II. Claim 12, drawn to piperazines, compounds of formula given in claim 1 with $C(O)NR^2R^3$ forming a 1-carbonylpiperidine, classified in class 546, subclass 175, among others.
 - III. Claims none, drawn to all other heterocyclic groups, compounds of formula given in claim 1 with $C(O)NR^2R^3$ forming all other heterocyclic groups, classified in class 540, subclass 470, among others.
 - IV. Claims 14, 16, and 17, drawn to complex compositions containing more than one active ingredient, classified in class 514, subclass 1 among others.

Claims 1-5, 7, 9, 11, 13, and 15 link Groups I-III.

If applicants elect group IV, the complex compositions, then they must also elect a species of antibacterial agents, antiviral agents, or antifungal agents for purposes of classification and examination.

If Applicants elect group III, then additional restriction will be required

3. The inventions are distinct, each from the other because of the following reasons: the heterocyclic core of the structure given in claim 1 is the ring formed by NR^2R^3 . This heterocyclic ring is a mandatory feature and range in size from four to nine atoms with multiple possible heteroatoms. These multiple claimed rings are chemically non-equivalent and are not art-recognized as sharing the same biological properties. Inventions I-III have acquired a separate status in the art as shown by their different classification, thus the patent search required for Group I is not co-extensive with that required for Groups II and III. The basic names of these heterocycles differ, thus the literature search for these various species will be divergent. Because these inventions are distinct for the reasons given above, restriction for examination purposes as indicated is proper.

Inventions IV and I-III are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because antibacterial agents, antiviral agents, and antifungal agents have therapeutic uses in addition to cancer treatment. The subcombinations I-III have separate claimed

utility such as treatment of multidrug resistance distinct from treatment of bacterial infections. Simple compositions and those with an additional active ingredient are patentably distinct because the combination (complex composition) can be patentable even if the subcombinations (the individual compounds) are not. This is because of the possibility of synergistic interaction, which is usually the purpose of the complex composition in the first place. Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification, and the search required for Group I-III is not required for Group IV, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Kelly McDow-Dunbar on 12/18/01 a provisional election was made with traverse to prosecute the invention of group II, claim 12 and parts of claims 1-5, 7, 9, 11, 13, and 15. Applicant in replying to this Office action must make affirmation of this election. Claims 6, 8, 10, 14, 16, and 17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be

accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Claims 1-5, 7, 9, 11, 13, and 15 are rejected on the grounds as being drawn to an improper Markush group *In re Harnisch* 206 USPQ 300. The claimed compounds, compositions, and methods that employ them present a variable core. Claim 1 contains compounds drawn to the non-elected rings formed by R^2 and R^{3+} .

Title

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacing "heterocyclic compounds" with "Piperidine Amide Containing Compounds".

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 9, 11, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "about 10", "about 4", and "about 9" in claim 1 are indefinite. Since the laws of chemistry require that atoms occur as indivisible units the variables w, x, and t must be whole numbers. The ring A must contain a positive whole number of

members. Does the phrase "about 10" mean ten or does it mean eleven? Could it mean twelve, thirteen, or fourteen?

9. Claims 1-5, 7, 9, 11, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "an active compound" in claim 1 is indefinite. It could be a statement of hope and given no patentable weight. It could be a structural limitation to the claim. If so, which compounds are not active and fit the claimed structure? The Examiner suggests deleting "active".

10. Claims 1-5, 7, 9, 11, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The words "heterogeneous group", "heterocyclic group", "heteroaromatic group", and "heteroatom" are indefinite. All are defined in the specification, except for the last, as containing a "hetero atom". In lines 9-12, page 4 there is an open definition of heteroatom. Are all non-carbon atoms included in this group? Is boron included? What about selenium or iodine?

11. Claims 1-5, 7, 9, 11, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly

claim the subject matter which applicant regards as the invention. Applicants repeatedly claim substituted carbocyclic, substituted heterocyclic etc. Substituted by what? The passage in the specification spanning line 25, page 5 to line 25, page 6 gives examples of such substituents as alkyl and alkoxy groups. Are any other substituents intended? Can a substituent be a hydroxyl, carboxyl, or halogen? Are there any limitations?

12. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 1 of the claim "the substituted heterocyclic group" is unclear. Does this refer to the heterocycle formed by the linking or R^2 and R^3 only? Are all the heterocycles found in groups R^1 - R^8 included?

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

- a. The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9, 11-13, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The

phrases “biohydrolyzable amide”, “biohydrolyzable ester”, and “biohydrolyzable imide” in claim 1 are unduly functional. What are the structures of these claimed compounds and how does determine if they are “biohydrolyzable”? It is not proper to describe compounds by their principal biological property, when more precise ways, i.e. names and structures are available.

14. Claims 1-5, 7, 9, 11-13, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of the formula of claim 1 with A = piperidine and $R^4-C(R^1)_2-R^5 = 2\text{-hydroxy-3-(5-quinolinyloxy)propyl}$, does not reasonably provide enablement for the myriad of heterocycles, heteroaromatic groups, and wide variety of linking groups provided for by the claims. The specification is not adequately enabled for the scope of compounds with variable x other than zero, i.e. absent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification is not adequately enabled for the scope of substituted hydrocarbon groups, substituted heterogeneous groups with nitrogen, sulfur, or phosphorus atoms. Compounds made and tested represent the scope of claim 12, not claim 1. There is no reasonable basis for the assumption that the myriad of compounds embraced the present claim 1 will all share the same biological

properties. The diverse claimed fused heteroaryl rings are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of cancer chemotherapy that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724.

15. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific human diseases, does not reasonably provide enablement for “inhibiting transport protein activity” generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This claim would read on transport protein activity inhibition in mammals with normal transport protein activity, in mammals with below normal transport protein activity, or in asymptomatic mammals with up-regulated transport protein activity. The specification fails to teach any benefit to be gained from such actions.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

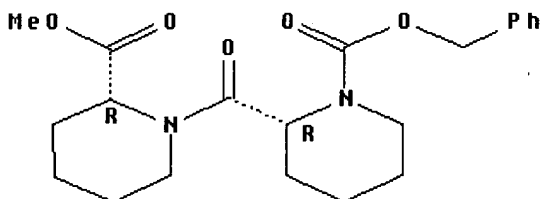
- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-

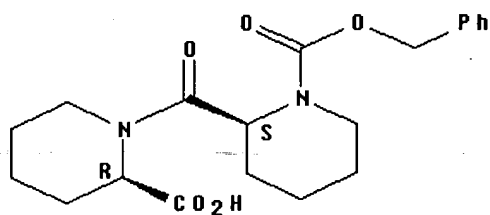
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent; except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

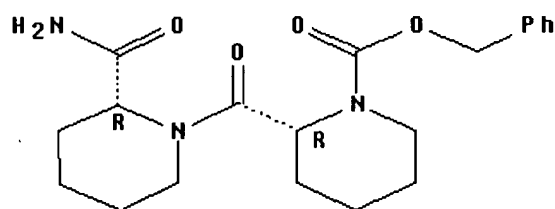
Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Vicar (Collect. Czech. Chem. Commun.). There are two compounds in this reference that anticipates Applicants compound claims, one of which is shown below. It has R^5 = benzyloxy, $r = 1$, R^6 = benzyl, $t = 0$, R^4 = C(O), A = piperidine, $x = 0$, and NR^2R^3 = 2-(methoxycarbonyl)-1-piperidinyl. The compound is described in Table I, page 4061 and is the penultimate compound.



17. Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Balaspiri (Acta Phys. Chem.). There are six compounds in this reference that anticipates Applicants' compound claims, one of which is shown below. It has R^5 = benzyloxy, $r = 1$, R^6 = benzyl, $t = 0$, R^4 = C(O), A = piperidine, $w = x = 0$, and NR^2R^3 = 2-(carboxy)-1-piperidinyl. The reference is not readily available so an abstract is provided.

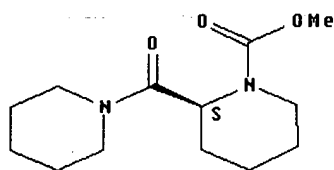


18. Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Kovacs (Pharmacol. Biochem. Behav.). There is one compound in this reference that anticipates Applicants' compound claims, which is shown below. It has R^5 = benzyloxy, $r = 1$, R^6 = benzyl, $t = 0$, R^4 = C(O), A = piperidine, $w = x = 0$, and NR^2R^3 = 2-aminocarbonyl-1-piperidinyl. The reference is not readily available so an abstract is provided.

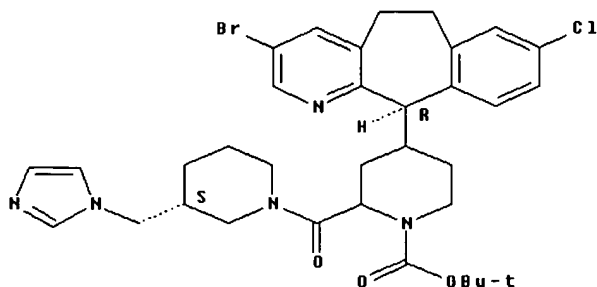


19. Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin (Tetrahedron Lett). There is one compound in this reference that anticipates Applicants' compound claims, which is shown below. It has R^5 = methoxy, $r = 1$, R^6 = methyl, $t = 0$, R^4 = C(O), A = piperidine, $w = x = 0$, and

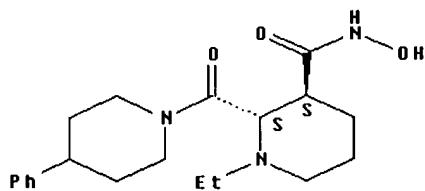
NR^2R^3 = 1-piperidinyl. The compound is described in the scheme on page 7181 and is compound 2, both optically active and racemic.



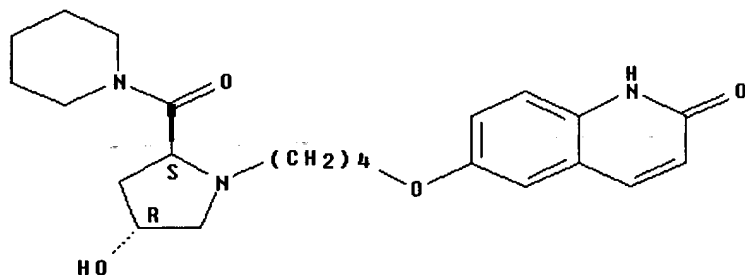
20. Claims 1-4, 13, and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Guzi (WO 00/37458). There are five compounds in this reference that anticipates Applicants compound claims, one of which is shown below. It has R^5 = butoxy, $r = 1$, R^6 = tert-butyl, $t = 0$, R^4 = C(O), A = piperidine, $w = 1$, R^8 = (11R)-3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl, $x = 0$, and NR^2R^3 = (3S)-3-(1H-imidazol-1-ylmethyl)-1-piperidinyl. The compound is described in Example 118, page 159. Please note, that if this publication ever issues as a US Patent, it will be a 102(e) reference because of the earlier effective filing date.



21. Claims 1-4, 11, 13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Xue (WO 99/65867). There are six compounds in this reference that anticipates Applicants compound claims, one of which is shown below. It has R^5 = ethyl, R^6 = methyl, $t = 1$, $R^4 = CH(R^1)$, R^1 = hydrogen, A = piperidine, $w = 1$, R^8 = N-hydroxy-3-carboxamide, $x = 0$, and NR^2R^3 = 4-phenyl-1-piperidinyl. The compound is described in the table on page 108 and is compound 75.




22. Claims 1-3, 11, 13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato ('239). There is one compound in this reference that anticipates Applicants compound claims, which is shown below. It has R^5 = 4-[(1,2-dihydro-2-oxo-6-quinolinyl)oxy]butyl, R^6 = (1,2-dihydro-2-oxo-6-quinolinyl)oxy, $r = 1$, $t = 3$, $R^4 = CH(R^1)$, R^1 = hydrogen, A = 4-hydroxy-2-pyrrolidinyl, $w = 1$, R^8 = 4-hydroxy, $x = 0$, and NR^2R^3 = 1-piperidinyl. The compound is described in Example 74, lines 31-45, column 70.



23. Claim 12 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Applicants' 2-hydroxy-3-(5-quinolinyloxy)propyl tails on ring A are novel over the prior art.

Conclusion

24. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.


Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
December 28, 2001



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